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1 **Original Article**

2
3 Prevalence of pancreatic, hepatic and renal pathology in post-mortem samples from
4 Cavalier King Charles Spaniels presented to a collection scheme

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24 **Abstract**

25 The Cavalier King Charles Spaniel is a common breed in the UK. Chronic valvular
26 disease and syringohydromyelia are frequently reported in this breed but there is less
27 information on other diseases despite a suspicion of over-representation.

28

29 The goal of this study was to describe the prevalence of pancreatic, hepatic and renal
30 pathology in Cavalier King Charles Spaniels presented to a pathology collection
31 scheme in the UK and to relate these back to the clinical signs shown during their
32 lifetime by evaluation of their clinical history.

33

34 54 dogs were available for analysis, ranging from 3 to 16 years of age and from 6 to
35 15.7 Kg in weight. The cause of death was most commonly congestive heart failure,
36 syringohydromyelia or other neurological disorders.

37

38 Evidence of chronic pancreatitis was seen in 51.9% of the cases, the age of dogs with
39 mild chronic pancreatitis was significantly lower than those dogs with more severe
40 disease. Evidence of renal pathology was present in 52.2% of cases, most commonly
41 inflammatory disease. The rate of ante-mortem diagnosis was low for both pancreatic
42 and renal disease, at 25% and 16.7% respectively.

43

44 Pancreatic and renal pathology are common in Cavalier King Charles Spaniels and
45 clinicians should be aware of this when presented with clinical cases.

46

47 *Keywords:* Chronic pancreatitis; Cavalier King Charles Spaniel; Renal; Hepatic;
48 Pathology

49 **Introduction**

50 The Cavalier King Charles Spaniel (CKCS) is a common breed in the United
51 Kingdom. The breed is commonly reported to suffer from chronic mitral valve disease
52 (Beardow et al., 1993) and syringohydromyelia (Rusbridge et al., 2000), however less
53 information exists on other pathologies, such as pancreatic, renal and hepatic disease,
54 although there is a suspicion of an increased prevalence of chronic pancreatitis in the
55 breed (Watson et al., 2007).

56

57 The Cavalier collection scheme (<http://www.thecavaliercollectionscheme.org>) was
58 initially started by motivated cavalier owners and breeders in collaboration, in order
59 to obtain post-mortem samples of the central nervous system from CKCS which had
60 had MRI prior to death to gain a better understanding of syringohydromyelia. It was
61 then extended to include samples of mitral valve for further studies of chronic
62 valvular disease. More recently, as increasing recognition of other diseases developed,
63 the scheme was extended again to include pancreatic, hepatic and renal samples.

64

65 Pancreatic, renal and hepatic diseases can be difficult to diagnose ante-mortem, due to
66 the non-specific nature of clinical signs, a lack of highly sensitive diagnostic tests and
67 variable disease progression. They can, however, cause significant morbidity in
68 affected dogs and so an indication of prevalence would be useful to help guide
69 clinicians to undertake appropriate diagnostic tests in living animals.

70

71 This study aimed to assess the prevalence of pancreatic, renal and hepatic pathology
72 in a population of CKCS presented to a post-mortem collection scheme and to relate
73 these back to the clinical history of those dogs. In addition, the study also aimed to

assess whether there was any statistically significant association between the different pathologies.

Materials and methods

The study aimed to take sections of pancreas, liver and kidney from the dogs presented to the Cavalier collection scheme by their owners with fully informed consent, however in a small number of dogs samples were only available for one or two of these organs. Some of these cases underwent a full post-mortem examination at the Department of Veterinary Medicine, University of Cambridge (DVMUC) whilst some cases had samples of the appropriate organs collected by veterinary surgeons in first-opinion practice in the UK. Full instructions were sent to the veterinary surgeons to ensure consistent sample collection (appendix 1). CNS samples were only taken if the dog had a post-mortem examination at DVMUC.

Each dog also required completion of the submission form for the collection scheme, which contained questions about relevant medical history. Some cases also had a full clinical history available. Medical history required included age and presence or absence of neurological signs, cardiovascular signs, gastrointestinal signs and any concurrent diseases (appendix 2 and 3).

All tissue samples were fixed in 10% neutral buffered formalin solution before being embedded in paraffin. The paraffin sections (5 μ m thick) were then stained with hematoxylin and eosin. Tissue sections were reviewed by two of the authors (P.J.W. and F.CC.).

Pancreatic pathology was categorised as previously published (Watson et al., 2007).

Chronic pancreatitis was defined as a lymphocytic or mixed inflammatory infiltrate (lymphocytes, plasma cells, macrophages, neutrophils) with or without fibrosis, with disruption of the normal pancreatic architecture. All of the pancreas sections were reviewed by one of the authors (P.J.W.) and allocated to one of the following categories:

- a) No evidence of chronic pancreatitis (Figure 1).
- b) Mild chronic pancreatitis: one or two small foci of lymphocytic infiltrate and fibrosis in the section examined (Figure 2).
- c) Moderate chronic pancreatitis: multi-focal areas of fibrosis and lymphocytes in the section examined but involving less than 50 per cent of area (Figure 3).
- d) Marked chronic pancreatitis: multi-focal areas of marked fibrosis and lymphocytic inflammation producing gross distortion of the normal architecture with less than 50 per cent of normal tissue remaining (Figure 4).
- e) “End-stage” was regarded as virtually no normal acinar tissue remaining (Figure 5).

The liver pathology was assessed according to the WSAVA standards for liver histopathology (ROTHUIZEN, 2006) and allocated to one of the following categories:

- a) No evidence of hepatic disease.
- b) Primary hepatic disease.
 - I. Chronic hepatitis: hepatocellular apoptosis or necrosis with an inflammatory infiltrate (mononuclear or mixed) and varying degrees of fibrosis.

124 II. Acute hepatitis: a combination of acute inflammation, hepatocellular
 125 apoptosis and necrosis, which may be accompanied by regeneration.
 126 III. Neoplasia.

127 c) Secondary hepatic disease

128 I. Hepatic congestion: engorgement and dilation of the hepatic veins and
 129 centrilobular sinusoids, which may be accompanied by dilated
 130 lymphatics and centrilobular perivenular fibrosis.

131 II. Hepatic vacuolation: hydropic change or fatty change (Figure 6).

132 III. Reactive hepatitis: inflammatory infiltrate in the portal areas or
 133 parenchyma with no hepatocellular necrosis.

134

135 Renal pathology was assessed into the following categories (Macdougall et al., 1986):

136 a) Normal

137 b) Inflammatory disease

138 I. Glomerulonephritis: proliferation of the endothelial and epithelial cells
 139 of the glomerular capillary with thickening of the glomerular basement
 140 membrane.

141 II. Interstitial Nephritis: a mixed inflammatory infiltrate of the
 142 interstitium

143 c) Other pathology

144

145 Dogs were excluded if neither a complete clinical history nor a complete submission
 146 form was available. Some cases did not have samples available from each organ.
 147

Dogs were considered to have had clinical signs that may have been consistent with chronic pancreatitis if they had frequently reported episodes of gastrointestinal signs (vomiting, diarrhoea, inappetence) or abdominal pain (Watson, 2012). A clinical diagnosis of renal disease was based on the identification of azotaemia, in the face of poorly concentrated urine (Lees, 2004).

Prevalence of pathology was calculated for each organ and compared to the prevalence of clinical signs. The signalment of dogs with or without pathology was compared by means of a Mann Whitney U test, the results were considered significant if $p < 0.05$. Relative risk was calculated for having renal disease together with chronic pancreatitis. It was considered significantly increased only if the risk and 95% confidence interval were greater than 1. Dogs with and without pancreatic pathology were compared for any significant differences in signalment.

Results

59 dogs were initially included in the study, 5 were subsequently excluded due to unavailable histopathology (2 dogs) or unavailable clinical history (3 dogs), leaving 54 dogs for analysis.

The dogs ranged from 3 to 16 years (mean 10.4 years, median 10.9 years) and from 6 to 15.7Kg in weight (mean 9.3Kg, median 9.3Kg). Dogs were euthanased or died for a number of reasons, including congestive heart failure (15 dogs), syringohydromyelia (10 dogs), other neurological disorders (11 dogs, most commonly degenerative myelopathy or seizures), neoplasia (6 dogs), renal disease (3 dogs), old

age (3 dogs), liver disease (2 dogs), pancreatic disease (2 dogs), and 1 each of severe anaemia and aggression.

18 dogs underwent a full post-mortem examination, the remainder had the relevant organs sampled by veterinary surgeons in practice. 12 dogs also had histopathology performed on the central nervous system, these have been reported as part of a previous study (Hu et al., 2012).

24 dogs (44.4%) were being treated for cardiac disease at the time of death with a number of medications including one or more of the following list: frusemide, pimobendan, spironolactone, benazepril, torsemide and digoxin. 25 dogs had an ante-mortem diagnosis of syringohydromyelia, some of which were receiving medical therapy including one or more of the following drugs: frusemide, gabapentin, prednisolone, non-steroidal anti-inflammatory drugs.

Pancreatic pathology was available for 54 dogs. 28 dogs (51.9%) had evidence of chronic pancreatitis, which was graded as mild in 10 dogs (35.7%), moderate in 13 dogs (46.4%), marked in 2 dogs (7.1%) and end-stage in 3 dogs (10.7%).

The median age of dogs with chronic pancreatitis was 11.1 years (range of 4 to 16 years) and without chronic pancreatitis was 9.7 years (range of 3 to 15 years), there was not a statistically significant difference ($p = 0.037$). The median weight of dogs with chronic pancreatitis was 9.75Kg (range of 6 to 13 Kg) and without chronic pancreatitis was 8.6Kg (range of 6.5 to 15.7 Kg), again there was no significant difference ($p = 0.407$).

197

198 When the age of dogs with mild chronic pancreatitis (n= 10, median 9.75 years) was
199 compared to a combined group of moderate, marked and end-stage chronic
200 pancreatitis (n= 18, median 13.0 years) there was a significant difference (p = 0.011).

201

202 Of the 28 dogs with evidence of chronic pancreatitis, only 13 (46.4%) were reported
203 to have clinical signs consistent with the disease prior to death and only 7 dogs were
204 diagnosed with chronic pancreatitis ante-mortem. In addition to these findings, one
205 dog without chronic pancreatitis had nodular hyperplasia and one dog with chronic
206 pancreatitis also had evidence of superimposed acute pancreatitis and pancreatic
207 necrosis.

208

209 Renal pathology was available for 46 dogs. 24 dogs (52.2%) had evidence of
210 abnormal pathology, most commonly glomerulonephritis (9 dogs) or interstitial
211 nephritis (10 dogs). Other abnormalities included tubular necrosis (1 dog), congestion
212 (1 dog), the presence of cysts (2 dogs) and steatosis (1 dog). Only 4 dogs (16.7%) had
213 a diagnosis of renal disease ante-mortem. The median age of the dogs with renal
214 disease was 12.0 years (range 3.0 to 16.0 years) and without renal disease was 10.25
215 years (range 4.0 to 15.5 years), this was not a statistically significant difference
216 (p=0.092).

217

218 Liver histopathology results were available for 54 dogs, this was most commonly
219 secondary pathology including congestion (12 cases), hepatocyte vacuolation (14
220 cases), hepatocyte vacuolation and congestion (8 cases), or reactive hepatitis (1 case).
221 Primary liver pathology was only identified in 6 cases and consisted of fibrosis (2

cases), cirrhosis (1 case) and chronic hepatitis (3 cases). One case had nodular hyperplasia. Two of the four dogs with chronic hepatitis and cirrhosis had an ante-mortem diagnosis of liver disease: one dog with cirrhosis and one dog with chronic hepatitis.

When considering inflammatory diseases, 8 dogs had both chronic pancreatitis and renal disease, 3 dogs had chronic pancreatitis and inflammatory liver disease and 1 dog had chronic pancreatitis, renal disease and inflammatory liver disease.

There was no increase in the relative risk of glomerulonephritis or interstitial nephritis in dogs with chronic pancreatitis (relative risk 0.8250, 95% CI 0.414 to 1.645, $p = 0.58$). There was also no increased risk of vacuolar hepatopathy in dogs with chronic pancreatitis (relative risk 0.6845, 95% CI 0.364 to 1.289, $p=0.24$). There was no increased relative risk of hepatic congestion in dogs with cardiac disease (relative risk 0.9900, 95% CI 0.508 to 1.928, $p=0.976$). Whilst the relative risk of inflammatory kidney disease was increased in dogs with cardiac disease (relative risk 1.3228, 95% CI 0.664 to 2.634, $p=0.43$), the confidence interval falls below 1 so it is unclear how significant the association is.

Discussion

This is the first study to examine the prevalence of histopathologically confirmed pancreatitis, renal and liver disease in a large population of CKCS examined at post-mortem. Whilst the prevalence of pancreatitis has been examined in previous studies (Newman et al., 2004, Watson et al., 2007), this is the first study to focus on only one breed of dog. This study shows the prevalence of chronic pancreatitis in the CKCS is

51.9%, which is greater than the 34% reported in a large study looking at post-mortem samples from a variety of different breeds (Watson et al., 2007). That study included 6 CKCS, all of which had evidence of chronic pancreatitis. The prevalence of renal disease was also very high in this study at 52.2% and yet the proportion of dogs which had ante-mortem diagnosis of either chronic pancreatitis or renal disease was very small.

Chronic pancreatitis is suspected to be an under-diagnosed disease, mainly due to the vague nature of the clinical signs (Watson, 2004) and that is supported by the results of this study. We found that only 24% of the cases with histological evidence of chronic pancreatitis had been diagnosed ante-mortem. This may be because the clinical signs were very intermittent, interpreted to represent an alternative disease or because the clinical signs were genuinely so subtle. However, chronic pancreatitis is known to be an important cause of chronic pain in dogs (Watson et al., 2010a, Bostrom et al., 2013) and in humans (Bouwense et al., 2013). The pain in humans results in a significant upregulation of central nociception, which is more marked the more severe the disease (Bouwense et al., 2013). It is possible that cavaliers with chronic pancreatitis suffer from chronic pain, which may be over-looked or confused in some cases with the pain of syringomyelia. It is therefore important for veterinary practitioners to be aware of chronic pancreatitis in cavaliers and to institute appropriate management including analgesics with the aim of reducing the morbidity.

The median age of dogs with more severe disease was greater than dogs with mild disease. This suggests that chronic pancreatitis is a progressive disease, which worsens with age.

272

273 This is the first study to report the prevalence of renal disease in Cavalier King
274 Charles Spaniels. Glomerulonephritis or interstitial nephritis was identified in 19 dogs
275 (41%) in this study, whilst only 4 dogs had an ante-mortem diagnosis of renal disease.
276 24 dogs (44.4%) in this study had congestive heart failure and were on long-term
277 medication for cardiac disease and this may mean that subtle changes in renal
278 function were overlooked. Many of the dogs were on medications that may have had
279 an impact on renal perfusion, for example angiotensin converting enzyme inhibitors
280 (ACEi) and diuretics and the assumption may have been that mild azotaemia was due
281 to reduced renal perfusion or the effects of diuresis. However, the changes identified
282 on pathology were indicative of primary renal disease in many dogs. It is likely that
283 the dogs with glomerulonephritis had measurable proteinuria and the dogs with
284 nephritis had poorly concentrated urine. However, the retrospective nature of these
285 samples means that we do not have comprehensive information on indicators of renal
286 function in most dogs. It is very important to increase recognition of chronic renal
287 disease in CKCS ante-mortem because there is strong evidence that changing dogs on
288 to a phosphate restricted diet formulated for renal disease can increase life-expectancy
289 by a factor of 3 (Jacob et al., 2002). However, clinicians also need to be aware that
290 renal diets generally have elevated fat concentrations, which may be problematic if
291 the dog also has chronic pancreatitis.

292

293 Hepatic pathology was commonly detected in this study but the majority of cases had
294 secondary findings likely to be related to other pathology. The finding of congestion
295 was assumed to be related to chronic heart disease. This was not supported by the
296 relative risk statistics, but sample size was small. The finding of hepatocyte

vacuolation is likely to be a secondary reactive change of the liver to a variety of other diseases. The prevalence of secondary hepatic pathology was very similar to that reported in a previous study in a number of breeds of dogs (Watson et al., 2010b).

The authors considered whether an association might exist between the different pathologies encountered. It was hypothesised that chronic pancreatitis might lead to an increased risk of glomerulonephritis due to the chronic inflammation and potential for immune complex deposition. Alternatively it was thought possible that chronic renal disease might cause pancreatitis, due to alterations in blood flow and an increase in circulating toxins. However in this study there was no increased risk of glomerulonephritis or interstitial nephritis in CKCS with chronic pancreatitis. It was equally considered that vacuolar hepatopathy may occur as a sequel to the chronic disease of chronic pancreatitis, however we found no evidence of an increased risk in this study. This agrees with a previous study (Watson et al. 2010b). That study did identify an increased relative risk of reactive hepatitis in dogs with chronic pancreatitis (Watson et al., 2010b). Only one dog in the current study was reported with reactive hepatitis so numbers were too small to investigate any potential association.

There are a number of limitations to this study. The first is the retrospective nature of the study, which meant that the CKCS had been exposed to a number of different therapeutic regimes ante-mortem, which may have impacted the pathology findings. The study was also reliant on owners to provide accurate clinical information which means that some information may have been missing. Investigating pancreatitis is also inherently difficult, as the pathology is not always uniformly distributed

throughout the organ. Lastly, the grading of pancreatitis is relatively subjective.

However all of the pancreas sections in this study were reviewed by one person,

which should allow some consistency of interpretation.

Conclusions

This is the first study to look at the prevalence of pathology of the liver, pancreas and kidney in the Cavalier King Charles Spaniel and it demonstrates a surprisingly high prevalence of chronic pancreatitis and renal disease in this breed (51.9% and 52.2% respectively), most of which were not diagnosed ante-mortem. Clinicians have in the past focussed on heart disease in the breed but should also be aware of the potential for these other diseases and consider them when confronted with clinical cases showing appropriate presenting signs. It is hoped that the results of this study will increase recognition and appropriate treatment of chronic pancreatitis and chronic kidney disease in Cavalier King Charles Spaniels, so improving the quality of life of affected dogs. Studies in the future should focus on understanding the reasons for these high disease prevalences in the breed.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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390
391

Figure legends

Fig. 1. Normal pancreas from a 10-year-old female CKCS. Most of the section consists of exocrine adenomeres with multiple pancreatic islets (arrows). H&E, bar: 300 μ m.

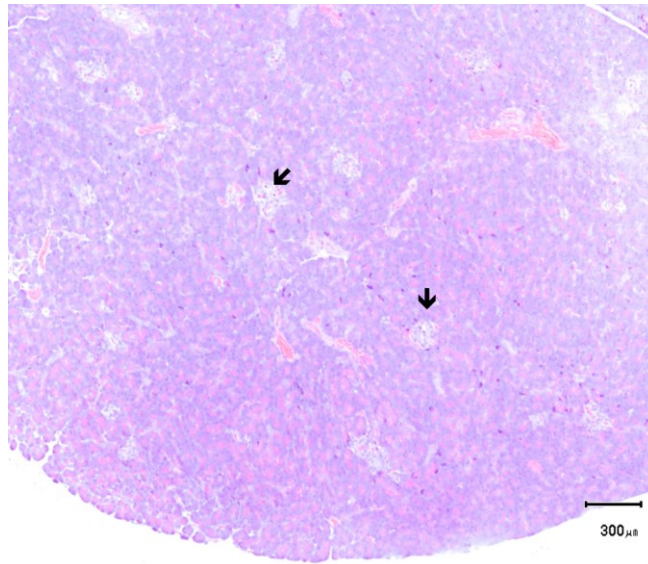


Fig. 2. Mild pancreatitis in a 12-year-old male CKCS, characterised by one area of dissecting fibrosis (F) with lymphocytic infiltrate. H&E, bar: 300 μ m.

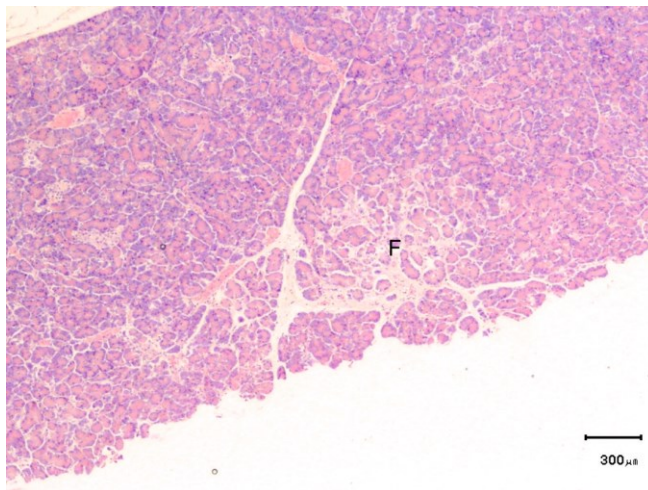
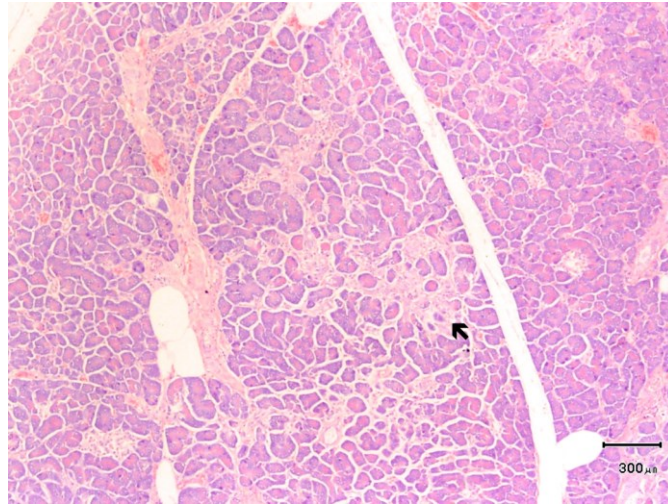
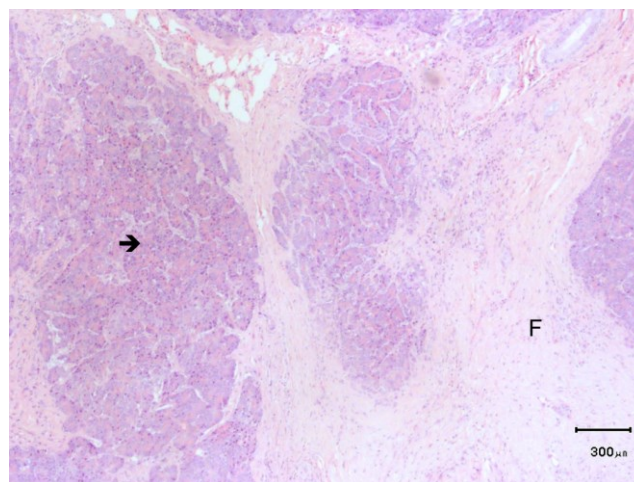


Fig. 3. Moderate pancreatitis in a 9-year-old male CKCS. Note multiple areas of dissecting fibrosis (arrow) with mononuclear inflammatory cells. H&E, bar: 300 μ m.



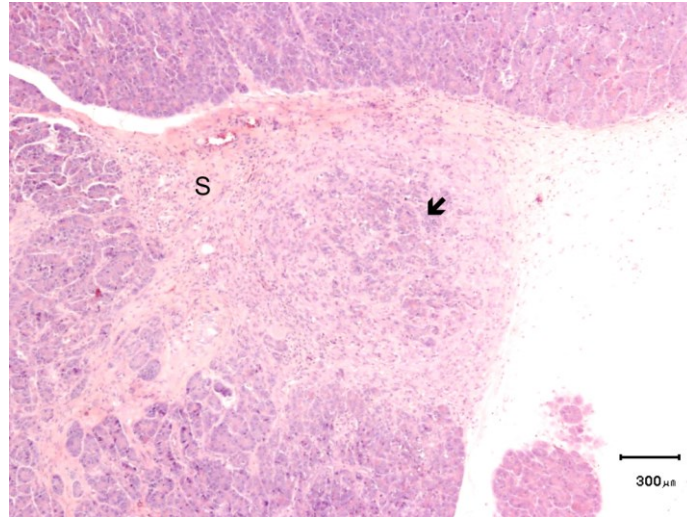
403

404 Fig. 4. Marked chronic pancreatitis in a 13-year-old female CKCS, note extensive
 405 fibrosis (F) containing lymphocytes surrounding remaining pancreatic tissue (arrow).
 406 The fibrosis takes up >50% of the section. H&E, bar: 300 μm.



407

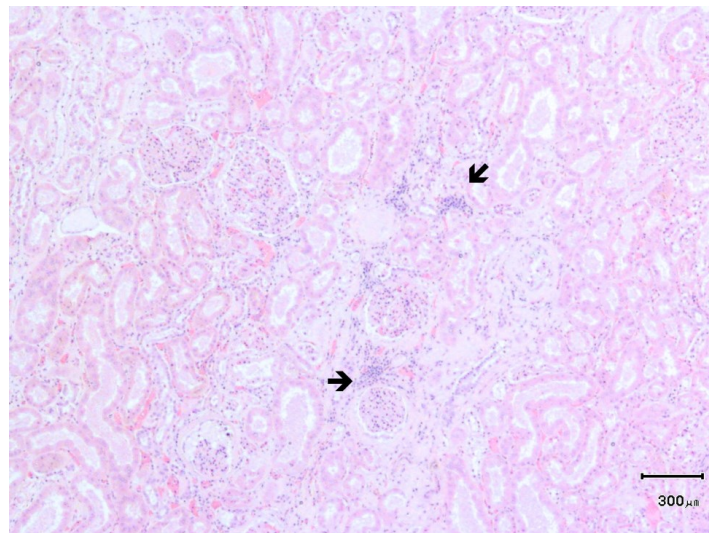
408 Fig. 5. Pancreas of a 16-year-old female CKCS with end stage chronic pancreatitis.
 409 Most of the pancreatic tissue has been replaced collagenous stroma admixed with
 410 blood vessels (S). Only a very small amount of remaining acinar tissue is found
 411 (arrow). The pancreas was not grossly visible at post mortem. H&E, bar: 300 μm.



412

413 Fig. 6. An example of a kidney of a CKCS with glomerulonephritis and interstitial

414 nephritis (arrows). H&E, bar: 300 μm.



415